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ISCHAEMIC HEART DISEASE

A ''no touch'' way to keep vein grafts patent ► Conventional harvesting of the saphenous vein during coronary artery bypass grafting surgery (CABG) causes damage to the vessel which has previously been shown to affect endothelial cell integrity and may therefore have an effect on the patency rate. To counteract this, a novel ''no touch'' technique has been engineered which involves harvesting the saphenous vein with its surrounding tissue. Souza *et al* assigned 52 patients to conventional CABG, while another 52 had their saphenous veins harvested using the ''no touch'' technique. Angiographic follow-up was performed at a mean time of 18 months after the operation in at least 45 patients from each group, and again at a mean time of 8.5 years in 37 patients from both groups. The recipient coronary arteries were similar in their size and quality in both groups. At 18 months 89% of conventional versus 95% of no-touch grafts were patent; at 8.5 years this difference widened to 76% and 90%, respectively (p = 0.01). By comparison, the patency of thoracic artery grafts was 90%. Multivariate analysis revealed that the two most important factors for graft patency were the technique of harvesting and the vein quality before implantation.

▲ Souza DS, Johansson B, Bojo L, *et al*. Harvesting the saphenous vein with surrounding tissue for CABG provides long-term graft patency comparable to the left internal thoracic artery: results of a randomized longitudinal trial. *J Thorac Cardiovasc Surg* 2006;**132**:373–8.

Enoxaparin in PCI ► Despite its limitations, unfractionated heparin has been the standard anticoagulant used during percutaneous coronary intervention (PCI). Several small studies have suggested that intravenous enoxaparin may be a safe and effective alternative. In this prospective, open-label, multicentre, randomised trial, the investigators randomly assigned 3528 patients with PCI to receive enoxaparin (0.5 or 0.75 mg/kg body weight) or unfractionated heparin adjusted for activated clotting time, stratified according to the use or non-use of glycoprotein IIb/IIIa inhibitors. The primary end point was the incidence of major or minor bleeding that was not related to CABG. Enoxaparin at a dose of 0.5 mg/kg was associated with a significant reduction in the rate of non-CABG related bleeding in the first 48 hours, as compared with unfractionated heparin (5.9% *v* 8.5%, absolute difference −2.6, 95% confidence interval (CI) −4.7 to −0.6; p = 0.01), but the higher enoxaparin dose was not (6.5% *v* 8.5%, absolute difference −2.0, 95% CI −4.0 to 0.0; p = 0.051). The incidence of major bleeding was significantly reduced in both enoxaparin groups, as compared with the unfractionated heparin group. So, in elective PCI, a single intravenous bolus of 0.5 mg of enoxaparin per kg is associated with reduced rates of bleeding, and a dose of 0.75 mg/kg yields rates similar to those for unfractionated heparin, with more predictable anticoagulation values. The trial was not large enough to provide a definitive comparison of efficacy in the prevention of ischaemic events. However, an accompanying editorial suggests that the safety of the 0.5 mg dose needs to be assessed further before recommending routine use.

▲ Montalescot G, White HD, Gallo R, *et al*, for the STEEPLE Investigators. Enoxaparin versus unfractionated heparin in elective percutaneous coronary intervention. *N Engl J Med* 2006;**355**:1006–17.

High dose statins reduce stroke risk in secondary prevention ► Statins reduce the incidence of strokes among patients at increased risk for cardiovascular disease; whether they reduce the risk of stroke after a recent stroke or transient ischaemic attack (TIA) remains to be established. The authors randomly assigned 4731 patients who had had a stroke or TIA within 1–6 months before study entry, had low density lipoprotein (LDL) cholesterol values of 100–190 mg/dl (2.6–4.9 mmol/l), and had no known coronary heart disease, to double-blind treatment with 80 mg of atorvastatin per day or placebo. The primary end point was a first non-fatal or fatal stroke. The mean LDL cholesterol value during the trial was 73 mg/dl (1.9 mmol/l) among patients receiving atorvastatin and 129 mg/dl (3.3 mmol/l) among patients receiving placebo. During a median follow-up of 4.9 years, 265 patients (11.2%) receiving atorvastatin and 311 patients (13.1%) receiving placebo had a fatal or non-fatal stroke (five year absolute reduction in risk 2.2%, adjusted hazard ratio 0.84, 95% CI 0.71 to 0.99; p = 0.03, unadjusted p = 0.05). The atorvastatin group had 218 ischaemic strokes and 55 haemorrhagic strokes, whereas the placebo group had 274 ischaemic strokes and 33 haemorrhagic strokes. The five year absolute reduction in the risk of major cardiovascular events was 3.5% (hazard ratio 0.80, 95% CI 0.69 to 0.92; p = 0.002). The overall mortality rate was similar, with 216 deaths in the atorvastatin group and 211 deaths in the placebo group (p = 0.98), as were the rates of serious adverse events. Elevated liver enzyme values were more common in patients taking atorvastatin (2.2% *v* 0.5%). The results contrast with those of the Heart Protection Study (HPS), which found no reduction in the risk of stroke among patients with prior cerebrovascular disease (10.4% of patients in the statin group had a recurrent stroke, as compared with 10.5% of patients in the placebo group). A possible explanation for this difference in results is that patients in the HPS were enrolled an average of 4.3 years after the index event, whereas the risk of recurrence is highest within the first years after stroke. Another explanation may be the larger reduction in LDL cholesterol in our study than in the HPS (56 mg/dl (1.4 mmol/l) *v* 39 mg/dl (1.0 mmol/l)).

▲ The Stroke Prevention by Aggressive Reduction in Cholesterol Levels (SPARCL) Investigators. High-dose atorvastatin after stroke or transient ischemic attack. *N Engl J Med* 2006;**355**:549–59.

The risk of smoking quantified ► The authors aimed to assess the risks associated with tobacco use (both smoking and non-smoking) and second-hand tobacco smoke (SHS) worldwide using a standardised case–control study of acute myocardial infarction (AMI) with 27 098 participants in 52 countries (12 461 cases, 14 637 controls). Current smoking was associated with a greater risk of non-fatal AMI (odds ratio (OR) 2.95, 95% CI 2.77 to 3.14; p < 0.0001) compared with never smoking; risk increased by 5.6% for every additional cigarette smoked. The OR associated with former smoking fell to 1.87 (95% CI 1.55 to 2.24) within three years of quitting. A residual excess risk remained 20 or more years after quitting (OR 1.22, 95% CI 1.09 to 1.37). Exclusion of individuals exposed to SHS in the never smoker reference group raised the risk in former smokers by about 10%. Smoking beedies alone (indigenous to South Asia) was associated with increased risk (OR 2.89, 95% CI 2.11 to 3.96) similar to that associated with cigarette smoking. Chewing tobacco alone was associated with OR 2.23 (95% CI 1.41 to 3.52), and smokers who also chewed tobacco had the highest increase in risk (OR 4.09, 95% CI 2.98 to 5.61). SHS was associated with a graded increase in risk related to exposure; OR was 1.24 (95% CI 1.17 to 1.32) in individuals who were least exposed (1–7 hours per week) and 1.62 (95% CI 1.45 to 1.81) in people who were most exposed (> 21 hours per week). Young male current smokers had the highest population attributable risk (58.3%, 95% CI 55.0% to 61.6%) and older women the lowest (6.2%, 95% CI 4.1% to 9.2%). Population attributable risk for exposure to SHS for more than one hour per week in never smokers was 15.4% (95% CI 12.1% to 19.3%).

▲ Teo KK, Ounpuu S, Hawken S, *et al*, for the INTERHEART Study Investigators. Tobacco use and risk of myocardial infarction in 52 countries in the INTERHEART study: a case-control study. *Lancet* 2006;**368**:647–58.

ACE inhibitors for all: coming back into fashion ► Angiotensin-converting enzyme (ACE) inhibitors reduce cardiovascular mortality and morbidity in patients with heart

failure or left ventricular systolic dysfunction (LVSD). Three large trials have assessed the effect of ACE inhibitors in stable patients without these conditions but with atherosclerosis. The authors undertook a systematic review of the Heart Outcomes Prevention Evaluation (HOPE), the European trial on Reduction Of cardiac events with Perindopril among patients with stable coronary Artery disease (EUROPA), and the Prevention of Events with ACE inhibition (PEACE) studies to determine the consistency with which ACE inhibitors reduce total mortality and fatal and non-fatal cardiovascular events. They computed cardiovascular outcomes and total mortality in the 29 805 patients of these three trials, randomly assigned an ACE inhibitor or placebo and followed up for a mean of about 4.5 years. The results were also analysed within the context of five large trials of ACE inhibitors in patients with heart failure or LVSD. When the findings of the HOPE, EUROPA, and PEACE trials were combined, ACE inhibitors significantly reduced all-cause mortality (7.8% *v* 8.9%; p = 0.0004), cardiovascular mortality (4.3% *v* 5.2%; p = 0.0002), non-fatal myocardial infarction (5.3% *v* 6.4%; p = 0.0001), all stroke (2.2% *v* 2.8%; p = 0.0004), heart failure (2.1% *v* 2.7%; p = 0.0007), CABG (6.0% *v* 6.9%; p = 0.0036), but not PCI (7.4% *v* 7.6%; p = 0.481). The composite outcomes of cardiovascular mortality, non-fatal myocardial infarction or stroke occurred in 1599 (10.7%) of the patients allocated ACE inhibitor and in 1910 (12.8%) of those allocated placebo (OR 0.82, 95% CI 0.76 to 0.88; p < 0.0001). Except for stroke and revascularisation, these results were similar to those of the five trials in patients with heart failure or LVSD. Therefore, use of ACE inhibitors should be considered in all patients with atherosclerosis.

▲ Dagenais GR, Pogue J, Fox K, *et al*. Angiotensin-converting-enzyme inhibitors in stable vascular disease without left ventricular systolic dysfunction or heart failure: a combined analysis of three trials. *Lancet* 2006;**368**:581–8.

Do patients with poor ventricular function always need an angiogram? ► Many patients with low ejection fraction also have coronary artery disease (CAD), but is there any way to separate those who need a coronary angiogram from those who do not? A retrospective analysis of the Duke databank for cardiovascular disease looked at 2054 patients who underwent cardiac catheterisation between 1992 and 2002 that was preceded by an echocardiogram with an ejection fraction of < 45%. The patients' median age was 63 years, and the median ejection fraction was 30%. A stenosis ⩾ 75% was considered to be significant. Overall 1184 (58%) patients had significant CAD and 870 (42%) did not. Significant predictors of CAD, in the order of their ability to predict significant CAD, were history of myocardial infarction, age, diabetes mellitus, having a Q wave on the ECG, male sex and segmental wall motion abnormality (all p < 0.0001). The authors suggest that given the high prevalence of patients without CAD in their cohort, an accurate baseline assessment of the likelihood of CAD in patients with poor left ventricular function may avoid the need for many unnecessary procedures.

▲ Whellan DJ, Tuttle RH, Velazquez EJ, *et al*. Predicting significant coronary artery disease in patients with left ventricular dysfunction. *Am Heart J* 2006;**152**:340–7.

HEART FAILURE

How does obesity cardiomyopathy occur? ► Obesity is a well-established risk factor for congestive heart failure, but the pathogenic mechanisms leading to the underlying myocardial alterations remain unclear. Di Bello's group in Pisa, Italy, used ultrasonic backscatter analysis (IBS) (an expression of increased myocardial collagen content) to look at subclinical alterations of left ventricular (LV) structure and function in severe obesity. Sixty severely obese patients (mean age 31.8 years) with no other medical problems were enrolled, while 48 age- and sex-matched controls were recruited as control patients. All underwent conventional two-dimensional colour Doppler echocardiography, pulsed wave Doppler tissue imaging at mitral annulus level, and IBS. Furthermore an insulin resistance index was used to assess insulin resistance in the two groups. Obese patients had a greater LV mass index by height (58.5 (14) $g/m^{2.7}$) than did the control subjects (37 (8) $g/m^{2.7}$; p < 0.0001) because of a compensatory response to volume overload caused by a greater cardiac output (p < 0.02). There were also significant increases in left atrial dimension (p < 0.0001) and LV ejection fraction (p < 0.03) in obese patients. Pulsed wave Doppler tissue imaging also showed an impairment of diastolic LV longitudinal function and increased LV diastolic filling pressure in obese patients. The IBS values at septum level were significantly higher for the septum in the obese group (57.8 (8)%) than in the control group (42.3 (9)%; p < 0.0001), and a significant association was found between the insulin resistance index and both the IBS index of myocardial reflectivity at septum level or LV mass. Therefore obese patients exhibit myocardial structural and functional alterations related to insulin resistance and to LV volume overload, which could be considered to be the beginning of incipient obesity cardiomyopathy.

▲ Di Bello V, Santini F, Di Cori A, *et al*. Obesity cardiomyopathy: is it a reality? An ultrasonic tissue characterization study. *J Am Soc Echocardiogr* 2006;**19**:1063–71.

GENERAL CARDIOLOGY

Body mass index predicts mortality ► Some doubt has been cast on whether body mass index (BMI) is an adequate measure of obesity. Waits measurement alone is suggested as an alternative. Obesity, defined by a BMI (weight in kilograms divided by the square of the height in metres) of 30.0 or more, is associated with an increased risk of death, but the relation between overweight (a BMI of 25.0 to 29.9) and the risk of death has been questioned. The authors prospectively examined BMI in relation to the risk of death from any cause in 527 265 US men and women in the National Institutes of Health–AARP cohort who were 50–71 years old at enrolment in 1995–96. BMI was calculated from self-reported weight and height. Relative risks and 95% CIs were adjusted for age, race or ethnic group, level of education, smoking status, physical activity, and alcohol intake. During a maximum follow-up of 10 years through 2005, 61 317 participants (42 173 men and 19 144 women) died. Initial analyses showed an increased risk of death for the highest and lowest categories of BMI among both men and women, in all racial or ethnic groups, and at all ages. When the analysis was restricted to healthy people who had never smoked, the risk of death was associated with both overweight and obesity among men and women. In analyses of BMI during midlife (age of 50 years) among those who had never smoked, the associations became stronger, with the risk of death increasing by 20–40% among overweight persons and by two to at least three times among obese persons; the risk of death among underweight persons was attenuated.

▲ Adams KF, Schatzkin A, Harris TB, *et al*. Overweight, obesity, and mortality in a large prospective cohort of persons 50 to 71 years old. *N Engl J Med* 2006;**355**:763–78.

But BMI falls down in meta-analysis ► Studies of the association between obesity and total mortality and cardiovascular events in patients with CAD have shown contradictory results. The authors selected cohort studies that provided risk estimates for total mortality, with or without cardiovascular events, on the basis of bodyweight or obesity measures in patients with CAD, and with at least six months' follow-up. CAD was defined as history of PCI, CABG, or myocardial infarction. They obtained risk estimates for five predetermined bodyweight groups: low, normal weight (reference), overweight, obese, and severely obese. They found 40 studies with 250 152 patients that had a mean follow-up of 3.8 years. Patients with a low BMI (< 20) had an increased relative risk (RR) for total mortality (RR 1.37, 95% CI 1.32 to 1.43) and cardiovascular mortality (RR 1.45, 95% CI 1.16 to 1.81), while overweight patients (BMI 25–29.9) had the lowest risk for total mortality (RR 0.87, 95% CI 0.81 to 0.94) and cardiovascular mortality (RR 0.88, 95% CI 0.75 to 1.02), compared with those for people with a normal BMI. Obese patients (BMI 30–35) had no increased risk for total mortality (RR 0.93, 95% CI 0.85 to 1.03) or cardiovascular mortality (RR 0.97, 95% CI 0.82 to 1.15). Patients with severe obesity (⩾ 35) did not have increased total mortality (RR 1.10, 95% CI 0.87 to 1.41) but they had the highest risk for cardiovascular mortality (RR 1.88, 95% CI 1.05 to 3.34). The better outcomes for cardiovascular and total mortality seen in the overweight and mildly obese groups could not be explained by adjustment for confounding factors. These findings could be explained by the lack of discriminatory power of BMI to differentiate between body fat and lean mass. The short duration of follow-up might also be relevant.

▲ Romero-Corral A, Montori VM, Somers VK, *et al*. Association of bodyweight with total mortality and with cardiovascular events in coronary artery disease: a systematic review of cohort studies. *Lancet* 2006;**368**:666–78.

Familial aortic dissection syndromes ► Dissection of the aorta may occur spontaneously even in normal sized aortas. A familial link is present in some cases. The Loeys-Dietz syndrome is a recently described autosomal dominant aortic aneurysm syndrome with widespread systemic involvement. The disease is characterised by the triad of arterial tortuosity and aneurysms, hypertelorism, and bifid uvula or cleft palate, and is caused by heterozygous mutations in the genes encoding transforming growth factor (TGF)-β receptors 1 and 2 (*TGFBR1* and *TGFBR2,* respectively). On the mild end, the mutations have been found in association with a presentation similar to that of Marfan's syndrome or with familial thoracic aortic aneurysm and dissection. From a study of a large cohort of patients and their families, the authors suggest that the natural histories of Loeys-Dietz syndrome type I and type II differ considerably from those of other connective tissue disorders. The median survival in their cohort was 37 years, as compared with 48 years among patients with vascular Ehlers-Danlos syndrome and 70 years among patients with Marfan syndrome who have been treated. The mean age at the first major vascular event in our group with Loeys-Dietz syndrome type II (29.8 years) is similar to that among patients with vascular Ehlers-Danlos syndrome caused by a deficiency of type III collagen (24.6 years). In both the Loeys-Dietz syndrome and vascular Ehlers-Danlos syndrome, dissection can occur without pronounced arterial dilatation. However, the incidence of fatal complications during or immediately after vascular surgery is about 45% in vascular Ehlers-Danlos syndrome but only 1.7% in Loeys-Dietz syndrome overall and 4.8% in type II. Thus, genotyping is beneficial in patients who present with features of vascular Ehlers-Danlos syndrome or Marfan syndrome. At least in mice with a Marfan-type syndrome, TGF-β signalling is returned to normal with losartan. A trial in humans is awaited.

▲ Loeys BL, Schwarze U, Holm T, *et al*. Aneurysm syndromes caused by mutations in the TGF-receptor. *N Engl J Med* 2006;**355**:788–98.

Ross procedure is safe long-term ► The use of the Ross procedure (pulmonary autograft replacement of the aortic valve) in adults remains controversial. Two hundred and sixty-four patients undergoing the Ross procedure in London and Rotterdam were followed up for a total of 1634 patient years; of these, 203 were men and 61 women, with a mean age of 35 years ranging from 18–66 years. The need for the procedure was due to congenital (52%), degenerative (22%) and rheumatic (8%) disease, and 21% of patients had undergone a prior aortic valve replacement. Overall 30-day mortality was 2.3% (n = 6), and four more patients died during follow up (mean follow up 6.2 years). Cumulative survival at five years was 96.8%, and at 10 years 95.4%. Ten patients had to undergo a further operation on the valve due to progressive dilatation and aortic regurgitation, and one due to arterial dissection of the wall of the homograft. Overall freedom from pulmonary homograft reoperation was 94.9% after 10 years, and for autograft reoperation was 92.9%. No risk factors for early or late mortality or reoperation were detected. The authors suggest that these excellent retrospective results mandate a prospective randomised trial to see whether their observations truly reflect the potential advantages of the Ross procedure, or whether they are caused by patient selection.

▲ Yacoub MH, Klieverik LM, Melina G, *et al*. An evaluation of the Ross operation in adults. *J Heart Valve Dis* 2006;**15**:531–9.

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IMAGES IN CARDIOLOGY

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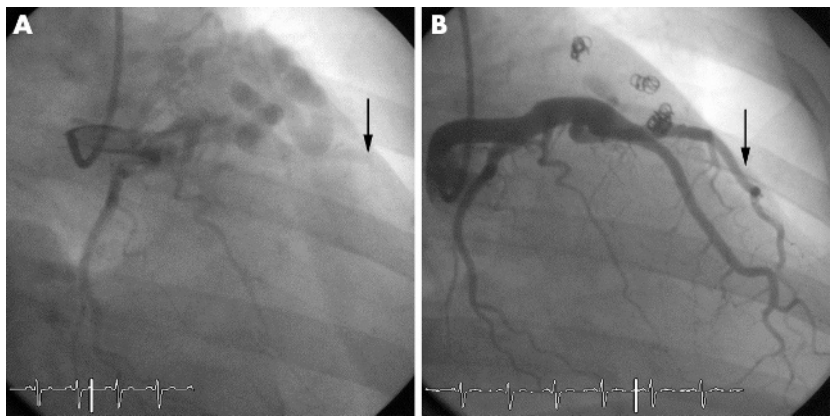
Percutaneous closure of a coronary to pulmonary artery fistula

A 54-year-old woman presented with a three year history of dyspnoea and chest pain on minimal exertion. Physical examination revealed a continuous murmur over the precordium. Background history included a cavernous haemangioma of the right lobe of the liver incidentally detected 10 years previously. Coronary angiography demonstrated a large fistula connecting the left anterior descending coronary artery (LAD) with the pulmonary artery (panel A). Very poor opacification of the LAD with dye injection was observed (see arrow in panel A). It was postulated that symptoms arose from a coronary steal effect and this was supported by myocardial perfusion imaging performed with adenosine stress which showed a reversible perfusion abnormality in the anterior wall of the myocardium. The fistula was occluded percutaneously by the deployment of 12 platinum coils (Trufill) into the fistula via the LAD. An instant improvement in dye opacification of the LAD was observed following the occlusion (see arrow in panel B) and corresponded with an immediate and dramatic improvement in symptoms.

A B Tokala
M Cowling
M G Gunning
ajaytokala@gmail.com



(A) Left anterior descending to pulmonary artery fistula. (B) Fistula occluded and flow restored in anterior descending artery.